

**Drawings:**

The drawing sheets attached in connection with the above-identified application containing new Figures 17A and 17B are being presented as new formal drawing sheets. Support for Figures 17A and 17B can be found on pages 36-39 of the subject application as originally filed. No new matter is added.

## REMARKS

### **Status of the claims**

Claims 1-87 were pending in the instant application with claims 1-28 under active consideration. With this Amendment, claims 29-87, which the Examiner has withdrawn from consideration, have been canceled without prejudice and may be pursued in divisional application(s). Claims 5, 8, 11, 12, 15 and 27 have been amended with this submission, and claims 88-100 have been newly added. Upon entry of this paper, therefore, claims 1-28 and 88-100 will be pending and under active consideration. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

### **Objection to the specification**

The specification has been objected to having figures/drawings as part of the specification, which the Examiner alleges should be in separate sheets. With this submission, the flowcharts on pages 36-39 have been re-presented as "Figure 17A" and "Figure 17B" and the specification appropriately amended to reference the figures. Hence, Applicants respectfully request that the objection to the specification be withdrawn.

### **Double patenting**

Claims 1-28 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6-9, 12-21, 23-34 of copending application no. 09/764,359. Though the conflicting claims are not identical, they are nonetheless alleged to be patentably indistinct from each other "because each [claimed invention] comprises methods of isolating liver progenitor cells comprising methods of fractionation by density centrifugation." The Examiner further alleges that "the use of percoll gradients for separation of cell populations from the liver [in the two disclosures]...would render the instant set of claims obvious over the other." Applicants respectfully traverse this rejection.

Traversal is based on the grounds that nothing in the art prior to the instant application taught a process of obtaining cells enriched in human liver cells, including hepatic stem and

progenitor cells by density centrifugation resulting in “two *bands* of cells separated by a density *barrier*” let alone “collecting the at least one band of *lower density*.” Namely, the process described in the cited art involved the use of *pellets*. What is more, Applicants respectfully note that the instant application discusses the use of the heretofore “standard” Percoll-based isolation method only by way of comparison of the instant invention. For example, see paragraphs 0051, 0061 and the discussion therebetween.

#### **Claim rejections under 35 U.S.C. § 112**

Claims 8 and 28 stand rejected under the second paragraph of 35 U.S.C. § 112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, each of these claims recite and encompass the use of trademark products. Applicants respectfully traverse these rejections.

The trademark recited in claim 8 is LIBERASE, a propriety mix of collagenases and neutral proteases commercially available from Roche. Without acquiescing to the propriety of the rejection, the claim has been amended accordingly.

Because claim 28 does not recite a trademark, Applicants have assumed that the Examiner may have intended to reject claim 27 on this ground, which claim does recite the trademark OPTIPREP. Applicants have deleted this mark from the claims.

Taken together, Applicants respectfully submit that the claim rejections have been rendered moot and respectfully request the withdrawal of same rejections.

#### **Claim rejections under 35 U.S.C. § 102**

Claims 1-7, 9-13, 15-21, 26 and 27 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending application no. 09/764,359. The Examiner alleges that “359 teaches methods of isolating liver progenitor cells comprising methods of fractionation by density centrifugation in particular the use of percoll gradients for separation of cell populations from the liver, in particular for the isolation of liver stem cells from primates such as humans.” Applicants respectfully traverse the rejection.

As mentioned above, Applicants respectfully note that the instant application discusses the use of the heretofore "standard" Percoll-based isolation method only by way of comparison of the instant invention. In other words, the discussion regarding Percoll in the instant application does not refer to the invention, but rather to what was practiced in the art at the time the application was filed. See paragraphs 0051, 0061 and the discussion therebetween.

For at least this reason, Applicants respectfully submit that the Section 102 rejection has been overcome and respectfully request its withdrawal.

### **Claim rejections under 35 U.S.C. § 103**

Claims 1-10, 12-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 682 106 A2, Gale et al. (J Endocrinol 92(2):293-302, Feb 1982), Singh et al. (Acta Physiol Scand 117(4):497-505, April 1983). Claims 1-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 682 106 A2 in view of Graham (Scientific World J 2:1347-50, May 2002). Graham teaches the use of iodixanol to generate a gradient to separate hepatic cells. Applicants respectfully traverse these rejections.

Applicants respectfully note that it is unclear on what basis the Examiner uses the EP reference, the Gale reference and the Singh reference in rejecting claims 1-10 and 12-26. In any event, the cited reference teach the use of Percoll gradients, which gradient teaches away from the instant invention. The following paragraph compares, in part, the instant invention from the Percoll gradients practiced at the time the invention was made:

[0061] These data clearly indicate that the novel OptiPrep™ fractionation method of the present invention separates live from dead cells while retaining viable hepatic stem/progenitor cells in the live fraction. In contrast, the standard method in the field, of centrifugation through a Percoll density gradient, excludes these cells from the pellet. While there are modifications in the conditions under which Percoll density gradients are run, all of these modifications involve short centrifugation times (minutes) and low g-force (50, 70, 88xg). The object of the conventional method appears to be enrichment for larger size, mature, viable hepatocytes. Since the Percoll pellet is used for all subsequent experiments (the supernate is discarded), the field has been consistently using cell preparations depleted of such proliferative stem/progenitor cells. Our novel method will most certainly change the types of experiments performed, and the data generated, to further advance the field.

Graham is cited in combination with the EP reference. It is not clear from the Office Action how the Examiner believes that the two references could be used in combination nor arrive at the instant invention. Nonetheless, Applicants respectfully submit that both references, alone or in combination, are silent with respect to silent “two *bands* of cells separated by a density *barrier* ... [wherein] at least one band of lower density...” is collected to obtain a population of cells enriched in viable human liver cells, including hepatic stem/progenitor cells.

For at least these reasons, Applicants respectfully submit that a prima facie case for obviousness has not been established. Accordingly, Applicants respectfully request the withdrawal of same rejections.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. § 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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